Aus dem Pathologischen Institut der Universität Basel
(Vorsteher: Prof. Dr. H. U. Zollinger)

Arbeit unter Leitung von P.-D. Dr. F. Gloor

MULTIPLE PRIMARY MALIGNANT NEOPLASMS IN BASEL 1951—1965

INAUGURAL-DISSERTATION

zur Erlangung der Doktorwürde der Medizinischen Fakultät
der Universität Basel

vorgelegt von

PETER A. GARUCCIO
von Long Beach, New York (U.S.A.)

Juris Druck + Verlag Zürich
1967

Aus dem Pathologischen Institut der Universität Basel
(Vorsteher: Prof. Dr. H. U. Zollinger)
Arbeit unter Leitung von P.-D. Dr. F. Gloor

MULTIPLE PRIMARY MALIGNANT NEOPLASMS IN BASEL 1951—1965

INAUGURAL-DISSERTATION

zur Erlangung der Doktorwürde der Medizinischen Fakultät
der Universität Basel

vorgelegt von

PETER A. GARUCCIO
von Long Beach, New York (U.S.A.)

Juris Druck + Verlag Zürich
1967

UNIV.
LEIDEN
BIBL.

Von der Medizinischen Fakultät genehmigt auf Antrag
von Prof. Dr. H. U. Zollinger.

Tag der Promotion: 21. Dezember 1967

Multiple primary malignant neoplasms were considered a rare and unusual medical curiosity when first described by Billroth in 1889 (6). Over the last fifty years, they have undergone a metamorphosis and are considered today to be a commonplace medical problem with which every practicing physician will be confronted. A difficult differential diagnosis is posed by the patient with cancer in whom signs and symptoms develop which suggest metastatic disease, when in fact a new primary neoplasm may have developed.

The steady increase of this phenomenon is best illustrated by the growth of reported cases during the last half century. Major reported a series of cases in 1918 of which 189 cases were considered as true examples of multiple neoplasm. (Warren and Gates). In 1921 Owens reported his series of 143 cases (20). A thorough search of the world literature by Warren and Gates in 1932 enabled them to compile 1,259 cases (30). Only thirty years later, Moertel reported in his Monograph that there are now more than 20,000 documented cases (17). Not only has the absolute number of cases reported grown, but the frequency of occurrence has also increased, and will continue to do so in the future, as the life span is lenghtend, and as more and more cancer patients are cured and survive long enough to develop another primary neoplasm.

CRITERIA FOR DIAGNOSIS

At the time Billroth first brought multiple primary malignant neoplasms to the attention of the medical world, he proposed three postulates for the authenticity of this finding. These are as follows.

1. Each tumor must have a different histologic appearance.
2. The tumors must arise in different locations.
3. Each tumor must produce its own metastasis.

Inasmuch as these conditions are not usually fullfilled, and are considered to be too rigid and unrealistic, they have been discarded in favor of the criteria advanced by Warren and Gates in 1932. These are as follows.

1. Each of the tumors must present a definite picture of malignancy.
2. Each lesion must be a distinct entity.
3. The probability that one was a metastatic lesion from the other must be excluded.

These postulates are considered more practical and have therefore been applied in this study.

SELECTION OF CASES FOR THIS STUDY

The material for this study was selected from 26,568 consecutive autopsies (including children and 291 leukemia necropsies) performed at the University of Basel, Institute of Pathology, during the 15 year period from 1951 through 1965.

Only those cases, in which a patho-histologic examination of each lesion had been made at this Institute were included.*) Patients with a history of a malignant neoplasm previously treated elsewhere without patho-histologic confirmation were excluded.

A concerted effort was made to ensure that the cases included represented true multiple malignant neoplasms. All cases which evoked reasonable doubt were excluded.

Lesions diagnosed within the same six month period were classified as "simultaneous lesions"; lesions diagnosed at intervals of longer than six months were classified as "interval lesions".

Not included in this study was multicentric carcinoma of the lung**), thyroid, pancreas and liver because of the problem encountered in establishing beyond reasonable doubt that these lesions are not metastatic from a single primary focus.

Carcinoma of paired organs (bilateral breast cancer and bilateral pulmonary carcinoma) was included only if there was a distinct difference in microscopic morphology. No cases of bilateral ovarian carcinoma have been included.

Multiple simultaneous gastric cancers were included only if a distinct histologic difference was demonstrable.

This series is a continuation of the earlier one of 6,188 cases of malignancy reported in 1952 by Albrecht (1), which covered the period from 1921 through 1950, and of the series of 644 cases of malignancy reported by Egli (9) in 1914 which covered the period from 1907 through 1913.

*) With the exception of two cases of malignant melanoma of the eye, where the histologic confirmation was made at the University Eye Hospital.

**) Three cases of multicentric carcinoma of the same lung were included only because a distinct histologic difference was demonstrable.

PRESENTATION OF DATA

Table 1 Incidence of Multiple Primary Malignant Neoplasma (MPMN)
A Comparison of the Three Basel Studies

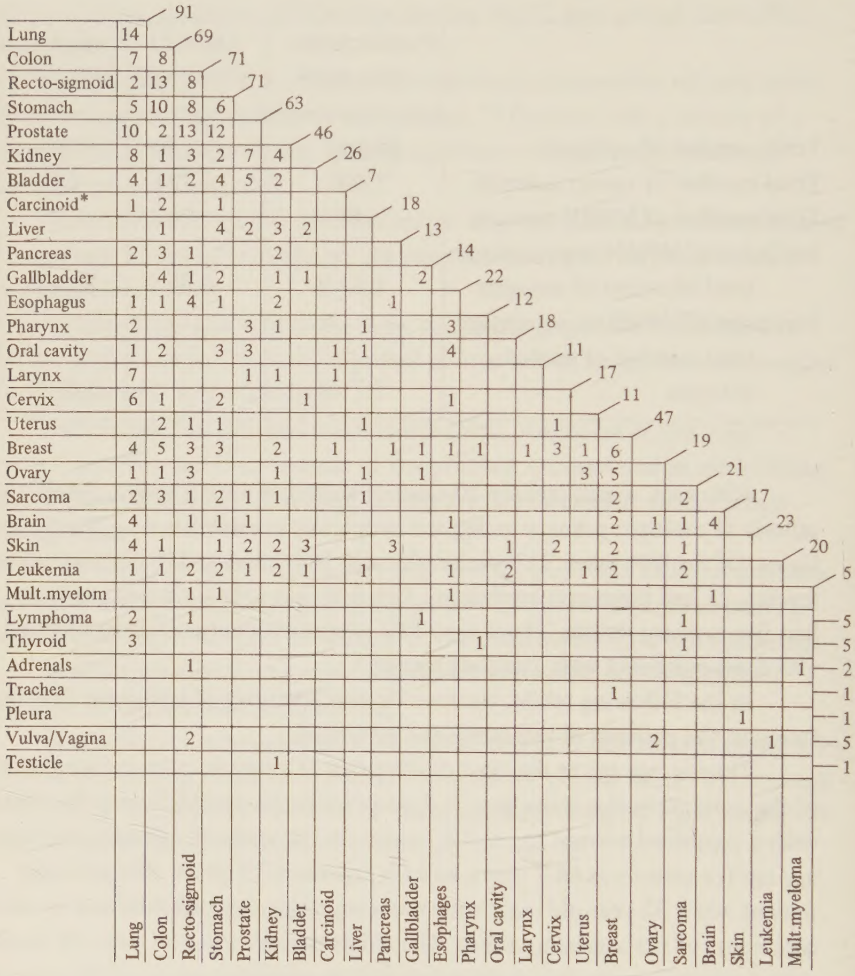
	Present Series 1951-1965	Albrecht 1921-1950	Egli 1907-1913
Total number of autopsis	26,568	31,630	4,765
Total number of cancer autopsis	7,005	6,188	644
Total number of MPMN autopsis	404	203	13
Incidence of MPMN in percentage total ofiumber of autopsis	1,52 %	0,64 %	0,28 %
Incidence of MPMN in percentage total number of cancer autopsis	5,7 %	3,3 %	2,0 %

404 cases, which include 20 cases of leukemia were found to fullfill the criteria of multiple primary malignant neoplasms as established by Warren and Gates. Of the 404 cases, 257 were males and 147 females. 376 had two primary lesions, 25 had three primary lesions, two had four primary lesions and one had five primary lesions. There were 840 separate primary malignant lesions. 193 cases presented with "interval lesions".

In the following tables, the specific combinations of malignant neoplasms found in the patients of this study are presented.

The average age at the time of diagnosis of multiple primary neoplasms of the patients in this series was 71.8 years for males and 68.9 years for females with a combined average age of 70.7 years. In the series of Albrecht, the average age for males was 66.7 years, and for females 67.9 years. The youngest patient was a 32 year old male with acute myelogenous leukemia and an adenocarcinoma of the ascending colon. The oldest patient was a 94 year old female with a carcinoma simplex of the breast and an adenocarcinoma of the stomach.

Table 2 Concurrence of Multiple Malignant Tumors. Cases with two lesions.



	Lung	Colon	Recto-sigmoid	Stomach	Prostate	Kidney	Bladder	Carcinoid	Liver	Pancreas	Gallbladder	Esophages	Pharynx	Oral cavity	Larynx	Cervix	Uterus	Breast	Ovary	Sarcoma	Brain	Skin	Leukemia	Mult.myeloma	
Lung	14																								91
Colon	7	8																							69
Recto-sigmoid	2	13	8																						71
Stomach	5	10	8	6																					71
Prostate	10	2	13	12																					63
Kidney	8	1	3	2	7	4																			46
Bladder	4	1	2	4	5	2																			26
Carcinoid*	1	2		1																					7
Liver		1		4	2	3	2																		18
Pancreas	2	3	1			2																			13
Gallbladder		4	1	2		1	1					2													14
Esophagus	1	1	4	1		2				1															22
Pharynx	2				3	1			1			3													12
Oral cavity	1	2		3	3			1	1			4													18
Larynx	7				1	1		1																	11
Cervix	6	1		2			1					1													17
Uterus		2	1	1					1								1								11
Breast	4	5	3	3		2		1		1	1	1	1		1	3	1	6							47
Ovary	1	1	3			1			1		1						3	5							19
Sarcoma	2	3	1	2	1	1			1									2		2					21
Brain	4		1	1	1							1						2	1	1	4				17
Skin	4	1		1	2	2	3			3				1		2		2		1					23
Leukemia	1	1	2	2	1	2	1		1			1		2			1	2		2					20
Mult.myelom			1	1								1									1				5
Lymphoma	2		1								1									1					5
Thyroid	3												1							1					5
Adrenals			1																					1	2
Trachea																		1							1
Pleura																						1			1
Vulva/Vagina			2																2				1		5
Testicle						1																			1

* Carcinoid tumors of the ileum

Table 3 Concurrence of Multiple Malignant Tumors. Cases with more than two lesions.

A. Cases with three lesions					number of cases	number of lesions
1. Lung	+	Colon	+	Stomach	2	6
2. Lung	+	Colon	+	Colon	1	3
3. Lung	+	Lung	+	Stomach	1	3
4. Lung	+	Larynx	+	Prostate	1	3
5. Colon	+	Colon	+	Colon	1	3
6. Colon	+	Rectum	+	Prostate	2	6
7. Colon	+	Rectum	+	Stomach	1	3
8. Colon	+	Breast	+	Lymphoma	1	3
9. Colon	+	Breast	+	Pancreas	1	3
10. Colon	+	Stomach	+	Prostate	1	3
11. Colon	+	Kidney	+	Kidney	1	3
12. Stomach	+	Prostate	+	Rectum	2	6
13. Stomach	+	Prostate	+	Pancreas	1	3
14. Stomach	+	Sarcoma	+	Esophagus	1	3
15. Stomach	+	Uterus	+	Cervix	1	3
16. Stomach	+	Kidney	+	Kidney	1	3
17. Rectum	+	Prostate	+	Bladder	1	3
18. Rectum	+	Rectum	+	Pancreas	1	3
19. Rectum	+	Kidney	+	Kidney	1	3
20. Prostate	+	Kidney	+	Brain	1	3
21. Pancreas	+	Ovary	+	Skin	1	3
22. Brain	+	Breast	+	Ovary	1	3
					25	75

B. Cases with four lesions						
1. Stomach	+	Stomach	+	Colon + Bladder	1	4
2. 2. Stomach	+	Rectum	+	Uterus + Cervix	1	4
					2	8

C. Cases with five lesions						
1. Rectum + Colon + Pharynx + Esophages + Oral cavity					1	5

Table 4 shows the age distribution of the present series, and the comparative findings in the series of Albrecht.

Table 4 Age Distribution of Multiple Primary Malignant Neoplasms

	Present series			Albrecht's series		
Age	Males	Females	Percentual distribution	Males	Females	Percentual distribution
30-39	1	3	1.0	1	-	0.5
40-49	7	9	4.0	2	6	4.0
50-59	31	23	13.3	24	12	17.7
60-69	65	35	24.7	44	16	29.6
70-79	93	51	35.7	46	25	35.0
80-89	56	24	19.8	15	9	11.8
90-99	4	2	1.5	1	2	1.4
	257	147	100.0%	133	70	100.0%

In comparing the findings of Albrecht with the present findings it becomes evident, that a percentual increase has occurred in the eighth decade which can be brought into context with the increasing longevity in our autopsy material. There is also an apparent peak incidence of multiple primaries during the seventh decade of life. This finding however, is misleading since it does not take into consideration the number of total autopsies and cancer autopsies performed in each age group. (Table 5).

In examening the at random chosen five year period from 1959 through 1963, and comparing the number of multiple primaries in each group with the number of necropsies performed, it may be concluded, that multiple primary malignant neoplasms are not more prevalent during the seventh decade. In fact, the percentage of multiple primary neoplasm autopsies performed between the fifth and eighth decade shows no appreciable change, hence, "old age" cannot be considered a primary factor in the etiology of multiple primary neoplasms. The accumulation of multiple primaries in the seventh decade is due to the fact that more necropsies are performed in that age group.

Table 5 Distribution of Necropsies, Cancer Necropsies and Multiple Malignant Tumor Necropsies performed in the various age groups. 1959 - 1963

Age groups	50-59y.	60-69y.	70-79y.	80-89y.	90-99y.
number of necropsies performed	1.068	1.784	2.102	1.452	154
number of cancer necropsies	232	564	525	325	24
% cancer necropsies performed	21.7	31.6	24.9	22.4	15.5
number of MPMN necropsies	21	49	56	36	2
% MPMN necropsies	2.0	2.8	2.7	2.4	1.3
Incidence MPMN in percent cancer necropsies	9.0	8.7	10.6	11.0	8.3

MPMN = Multiple primary malignant neoplasms

The age distribution of the 25 cases presenting with three primary malignant neoplasms is as follows.

Age	60 - 69 years	4 males	1 female
	70 - 79 years	6 males	2 females
	80 - 89 years	8 males	3 females
	90 - 99 years	1 male	-

The average age in this group was 78.4 years for males and 76.6 years for females. This seems to support the conclusion reached by Egli in 1914 when he stated: "The more tumors that are found in a cadaver, the older the patient was."

The sex distribution in this series is 257 males and 147 females, a ratio of 1.7 to 1 or a 63 % male preponderance. Albrecht reported a ratio of 2.0 to 1, Warren and Ehrenreich 2.1 to 1 and Moertel 1.5 to 1. All show a preponderance of the male sex. This can be brought into context with the fact that male cancer autopsies are more common. At the Institute of Pathology of the University of Basel, the following autopsy ratios are found.

Total autopsies: a ratio of 1.1 to 1, or a 52 % male preponderance.
Total cancer autopsies: a ratio of 1.4 to 1 or a 59 % male preponderance, with a range of 54 % to 64 % for any given year.

DISCUSSION

Location of Lesions

A high incidence of multiple primaries associated with carcinoma of the colon and rectum has been reported by Polk and Tullis. (21, 28). This has also been the finding in this series where lesions of the colon and rectum comprise the major group (approx. 20%). The frequent involvement of the female breast and genitalia in multiple primaries has been reported by Moertel Taylor and Bachulis (3, 17, 27). In this study, these lesions comprise the second largest group with 13 % of all lesions. The location of multiple primary lesions in the various studies depends upon the source of clinical material. Malignant skin lesions comprised the major group in the report of Hurt and Broders (11). In the present study however, they make up only a small percentage (less than 3 %) because of the difficulty in keeping and obtaining accurate records of the outpatient excisions of these lesions, since they are not custemarily examined at this Institute, but at the University Dermatology Clinic. The lung was found to be the third most common site of lesions.

In comparing the distribution of lesions in Albrecht's series with the present study (Table 6) it is notable that lung lesions showed a percentual increase from 5.2 % to 11.5 %, whereas lesions of the stomach decreased from 14.7 % to 10.1 %. The distribution of single malignant neoplasms at this Institute shows a comparative increase of lung cancer and decrease of stomach cancer (23).

Kuehn (13) supports the contention that if a patient develops cancer within a specific tissue, the second primary lesion is very likely to develop within the same type of tissue. This could be substantiated by this study for lesions of the gastro-intestinal tract, female genital tract, and to a lesser degree for the respiratory tract. The findings are tabulated below.

Table 6 Distribution of lesions by site

	Present study		Albrecht	
	Lesions	Percentage	Lesions	Percentage
Colon & Rectum	167	19.9	71	16.8
Breast & Female Genitalia	108	12.6	55	13.1
Lung	97	11.5	22	5.2
Stomach	85	10.1	62	14.7
Urinary tract	81	9.7	46	10.9
Male genitalia	73	8.7	45	10.6
Oropharynx, Larynx and Trachea	45	5.4	14	3.3
Liver & Gallbladder	32	3.9	18	4.3
Reticuloendothelial syst.	31	3.8	-	-
Esophagus	24	2.9	35	8.2
Skin	24	2.9	4	0.9
Sarcomas	22	2.7	13	3.1
Brain	19	2.2	9	2.3
Pancreas	17	2.0	10	2.6
Miscellaneous	15	1.7	17	4.0
	840	100.0	421	100.0

Table 7 Location of second primary malignancy in patients with a primary malignancy located in the colon and rectum

Total number of cases:	134	=	100.0 %
Second primary malignancy located			
in gastro-intestinal tract	54	=	40.3 %
in prostate	20	=	14.9 %
in female genitalia	19	=	14.8 %
in respiratory tract	12	=	8.9 %
in urinary tract	11	=	8.8 %

Table 8 Location of second primary malignancy in patients with a primary malignancy located in the female genitalia (excluding Breast lesions)

Total number of cases:	55	=	100.0 %
Second primary malignancy located			
in female genitalia	15	=	27.3 %
in gastro-intestinal tract	10	=	18.2 %
in respiratory tract	7	=	12.8 %
in female breast	9	=	16.4 %

Table 9 Location of second primary malignancy in patients with a primary malignancy located in the larynx

Total number of cases:	12	=	100.0 %
Second primary malignancy located			
in lung	8	=	66.7 %

These findings point out the probability that a common factor, be it an external carcinogen, or an inherited susceptibility to tumor formation may be the causative agent in multiple tumors of the same organ system.

Multiple lesions of the same organ and of paired organs.

Multiple primary tumors of paired organs and multiple primary tumors of the same organ were included in this study only after careful scrutiny to eliminate the possibility of including metastatic lesions from a single primary focus. The findings are shown in Table 10 and Table 11.

Table 10 Multiple carcinoma of paired organs

Breast	3 cases
Lung	5 cases
Kidney	5 cases

Table 11 Multiple carcinoma of the same organ

Colon and Rectum	28 cases
Stomach	4 cases
Lung/Bronchus	3 cases
Brain	2 cases

In multiple primary lesions of the colon and rectum, the microscopic findings were more often than not alike. The diagnosis of multiple colonic carcinoma was therefore accepted on the basis of the following criteria as proposed by Moertel (17).

1. Each lesions must be of pathologically proved malignancy
2. All lesions must be distinctly separated.
3. The possibility that one of the lesions represents a local extension or metastasis must be ruled out.

Twenty-eight cases presented with more than one primary lesion in the colon and/or rectum. These comprised 57 separate lesions which were distributed as follows: 26 lesions in the recto-sigmoid, 17 lesions in the coecum and ascending colon, 6 lesions in the transverse colon and 8 lesions in the descending colon. One of these cases had three primary lesions in the colon: A mucin producing adenocarcinoma of the transverse colon which was excised in 1931. Thirty years later this patient presented with a mucin producing adenocarcinoma of the ascending colon and a non-mucin producing adenocarcinoma of the descending colon.

The four cases of multicentric carcinoma of the stomach were included in this study only because histologically different primary lesions were distinguishable.

Eight cases with two primary lesions in the lungs are also presented. Only those cases presenting a distinct difference in microscopic morphology between the two primary lesions were considered acceptable. Of the eight cases, five had one primary lesion in each lung, and three had both primaries in the same

lung. In five cases the interval was less than one year, in the other three cases it ranged from 4 years to 9 years.

Three cases of bilateral breast cancer are reported in this series. In order to avoid the controversy whether the second breast lesion is actually a primary focus or merely a metastatic focus of the first lesion, only cases with different histologic morphology between the first and second lesion were included. The interval between the first primary lesion and the second primary lesion in the reported three cases was 5 years, 6 years and 23 years respectively.

Of the five cases of bilateral primary kidney neoplasm, four presented with bilateral renal carcinoma (hypernephroma), the fifth with a bilateral renal pelvis neoplasm. Several cases of unilateral multicentric renal carcinoma were not included because of the difficulty in demonstrating that these were true multicentric lesions and not local metastatic lesions.

Both cases of multicentric carcinoma of the brain had as the initial primary lesion a malignant meningeoma; one in conjuction with an astrocytoma after an interval of two years, the other in conjunction with a neurospongioma with an interval of less than six months.

Leukemia plus malignant lesions

The coexistence of leukemia with another malignant lesion has at one time been considered a rare entity. Morrison (18) reported in 1944 two cases in a series of 600 leukemia patients, an incidence of 0,33 %. Moertel (17) reported 2,134 cases of leukemia seen at the Mayo clinic. In 52 of these leukemia patients an associated primary malignant lesion was found; an incidence of 2.4 %. In this study, twenty patients out of a total of 291 leukemia autopsies were found to have a co-existing primary malignant lesion; an incidence of 6.9 %. This incidence is somewhat higher than that reported by Moertel, but he feels that the true incidence is provided by a study of those patients with leukemia on whom post-mortem examinations were performed. In Moertel's series 204 of his cases came to autopsy and in seventeen of these, an associated malignant lesion was found; an incidence of 8.3 %. There is no evidence that leukemia predisposes to the development of any other specific type of primary malignancy. Moertel concluded that the incidence of another primary malignant lesion in patients with leukemia is probably comparable to and perhaps exceeds that in any segment of the general population. This study seems to support this conclusion.

At one time, several authors, (19, 24, 32) supported the contention that multiple primary malignant neoplasms were a chance occurrence which manifests itself at an advanced age. Stalker (26) stated "we do not believe that the prevalent impression, that multiple malignant lesions occur more often at an advanced age than do single malignant lesions is based on adequate data". The present study also shows no significant increase of multiple primary malignant lesions in the older age groups (Table 5), hence, the contention that advanced age is a primary factor in the etiology of multiple primary malignant neoplasms must be discarded.

The majority of authors (7, 14, 29, 30) agree that the actual incidence of the development of multiple primary malignant neoplasms is significantly higher than could be expected on the basis of chance alone, and many statistical studies have been published to support this contention. Lombard and Warren (14) found in a study of 1990 patients with primary carcinoma that 117 of these developed a second primary cancer, which exceeded the calculated expected number of 80 to 85. They concluded that the presence of one cancer does not confer immunity, but, on the contrary, that patients with one cancer are more susceptible to the disease than are individuals who have never had one. This implies the presence of a definite predisposition or suceptibility to malignancy or to the action of some factor favoring the development of malignancy.

Heredity may play a part in the occurrence of these multiple malignancies. In the series of cases reported by Hurt and Broders (11), there was a significant family history of cancer in 28.6 %. In the review of Stalker (26) a family history was derived in 26.6 %. Kirshbaum and Shively (12) on the basis of their individual data, conclude "individuals may be endowed with a congenital, or acquired, predisposition toward tumor formation". Lynch (15), in his study of six cancer families even speaks of a hereditary multiple cancer syndrome, wherein the carcinogens require a susceptible host and where this suceptibility is under mendelian inheritance control. The incidence of multiple primary malignancies in these cancer families varied from 13.5 % to 33.3 % with a mean of 18.7 %; this being three times as great as the incidence of multiple primary malignancy which is generally reported to be from 4 to 6 percent. A study aimed at the familial occurrence of cancer in this series was omited owing to a lack of sufficient clinical data.

Incidence of Multiple Primary Malignant Neoplasms

The patient with multiple primary malignancies has ceased to be a medical and pathological curiosity. As shown by numerous clinical and autopsy studies, the incidence of this phenomenon is higher than commonly realized and has grown in excess of the analagous increase of carcinoma in general. This increased incidence is best illustrated by comparing the incidence of multiple neoplasms in studies done at various time at the same three institutions using the same method of diagnosis as shown in Table 12.

Table 12 Incidence of new primary malignant neoplasms in patients with malignant tumors

Author	Year	Method of Diagnosis	Institution	Number of Cancer Patients	Incidence of MPMN
Warren	1932	Necropsy	New England Deaconess Hospital etc.	1,078	3.7 %
Warren	1944	Necropsy	- " -	2,829	6.8 %
Hurt and Broders	1929	Clinical Findings & Necropsy	Mayo Clinic	2,124	3.3 %
Stalker	1939	- " -	- " -	2,500	4.5 %
Moertel	1961	- " -	- " -	37,580	5.1 %
Egli	1914	Necropsy	Univ. of Basel	644	2.0 %
Albrecht	1952	- " -	- " -	6,188	3.3 %
Present series	1967	- " -	- " -	7,005	5.7 %

As has already been pointed out by various authors (Baldwin, Fried, Werthamer), this increase is ascribable to better diagnostic and pathologic examination, longer life in general and after cancer therapy in particular, and possibly to increased exposure to carcinogenic stimuli, including diagnostic and therapeutic irradiation.

SUMMARY

In the fifteen year period from 1951-1965, 26,568 consecutive autopsies (including children) were performed at the University of Basel, Institute of Pathology. Of these, 7,005 were cancer autopsies and in 404 of these multiple primary malignant tumors were observed. The incidence was 5.7 % of all cancer autopsies. There were more males than females, the ratio being 1.7 to 1. The gastro-intestinal tract in general, and the colon and rectum in particular were the most common site of lesion.

The phenomenon of multiple primary malignant neoplasms is more prevalent today than fifty years ago. This is demonstrated by comparing the present study with studies done at this institute beginning with 1914. The steady increase of this phenomenon may be attributed to better diagnostic and pathologic examination, increased longevity and increased exposure to carcinogenic stimuli.

The incidence of a primary malignant lesion in patients with leukemia was 6.9 %.

A primary lesion in one organ system predisposes to the formation of a subsequent primary lesion of the same organ system. This was shown to be true for the gastro-intestinal tract, female genital system and to a lesser degree for the respiratory system. This may be due to the action of some common factor such as external carcinogens or inherited susceptibility to tumor formation in a particular organ or organ system.

Multiple primary tumors are most common during the sixth and seventh decade of life. Single carcinomas are most common during the sixth decade. Triple primary lesions occur at a later stage of life, being most frequent in the eighth decade.

Every physician is obliged to carefully evaluate a cancer patient who presents with signs and symptoms of metastasis to rule out the possibility of a new primary malignancy.

REFERENCES

1. ALBRECHT, P.: Über die Multiplizität primärer maligner Geschwülste, Oncologia 5:12 (1952)
2. ANDERHUB, V.: Über Multiplizität primär bösartiger Geschwülste. Inaug. Diss. Zürich (1937)
3. BACHULIS, B.L. and WILLIAMS, R.D.: Multiple primary malignancies. Arch. Surg. 92:537 (1966)
4. BALDWIN, J.N.: Multiple primary neoplasms. Am.J.Surg. 111:230(1966)
5. BAUER, K.: Das Krebsproblem. Springer-Verlag, Berlin-Heidelberg. (1952)
6. BILLROTH, T.: Die Allgemeine Chirurgische Pathologie und Therapie. 14. Aufl. G. Reimer, Berlin. (1889)
7. BUCHER, J.C.: Probability of chance occurrence of multiple malignant neoplasms. Am.J.Cancer 21:809 (1934)
8. BURKE, M.: Multiple primary cancers. Am.J.Cancer 27:316 (1936)
9. EGLI, E.: Über Multiplizität. Inaug.Diss. Basel (1914)
10. FRIED, B.M.: cited by Baldwin, J.N. loc.cit.ref. 4
11. HURT, R.E. and BRODERS, A.C.: Multiple primary malignant neoplasms. J.Lab.clin.Med. 18:765 (1933)
12. KIRSHBAUM, J. and SHIVELY, F.: Multiple primary malignant tumors. J.Lab.clin.Med. 24:283 (1938)
13. KÜHN, P.G., BECKETT, R. and REED, J.F.: Tissue specificity in multiple primary malignancies. Am.J.Surg. 111:164 (1966)
14. LOMBARD, H.L. and WARREN, S.: Association of other malignant tumors with cancer of the skin. Am.J.Pub.Health. 33:533 (1943)
15. LYNCH, H.T.: Hereditary factors in carcinoma. Recent results in cancer research. Springer Verlag, Berlin-Heidelberg, Vol. 12. (1967)
16. MCGRATH, E.J.: Bronchogenic carcinoma; a product of multiple sites of origin. J.Thorac. Surg. 24:271 (1952)
17. MOERTEL, C.: Multiple primary malignant neoplasms. Recent results in cancer research. Springer-Verlag, Berlin-Heidelberg, Vol.7 (1966)
18. MORRISON, M., FELDMAN, F. and SAMWICK, A.: Carcinoma and leukemia: Report of two cases with combined lesions; review of literature. Ann.intern.Med. 20:75 (1944)
19. MÜLLER, A.: Cited by Albrecht, P. loc.cit.ref. 1.
20. OWEN, L.J.: Multiple malignant neoplasms. J.Am.Med.Assoc. 76:1329 (1921)

21. POLK, H.C., SPRATT, J.S., and BUTCHER, H.R.: Frequency of multiple primary malignant neoplasms associated with colorectal carcinoma. Am.J.Surg., 109:71 (1965)
22. SHIELDS, T.: Bilateral primary bronchogenic carcinoma. J.Thorac.Surg. 48:401 (1964)
23. SCHOTTLAND, E.: Bronchialcarcinom. Inaug.Diss.Basel (1966)
24. SIEBKE, H.: Über Multiple Karzinose. Zt.f. Krebsforschung. Bd.23:66 (1926)
25. SLAUGHTER, D.: The multiplicity of origin of malignant tumors. Int. Abstr.Surg. 78:89 (1944)
26. STALKER, L.E., PHILLIPS, R.B. and PEMBERTON, J.: Multiple primary malignant lesions. Surg.Gynec.Obstet. 68:595 (1939)
27. TAYLOR, H.C.: Coincidence of primary breast and uterine cancer. Am.J.Cancer 15:277 (1931)
28. TULLIS, J.: Multiple primary malignant lesions. J.Lab.clin.Med. 27:588
29. WARREN, S. and EHRENREICH, T.: Multiple primary malignant tumors and susceptibility to cancer. Cancer Res. 4:554 (1944)
30. WARREN, S. and GATES, O.: Multiple primary malignant tumors; A survey of the literature and a statistical study. Am.J. Cancer 16: 1358 (1932)
31. WERTHAMER, S., JABUSH, M. and SCHULMAN, J.: Cited by Baldwin, J.N. loc.cit.ref. 4.
32. VIRCHOW, R.: Cited by Albrecht, P. loc.cit.ref. 1.